THE PREPARATION OF POTENTIALLY PSYCHOACTIVE β-ALKOXYPHENETHYLAMINES

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Abstract. The preparation of β-alkoxyphenethylamines 3 is described.

As part of our interest in structure-activity relationships of psychotomimetic phenethylamines 1 and their interactions with serotoninergic receptors 2, we describe in the present communication the preparation of a series of substituted β-alkoxyphenethylamines.

A few of these compounds had been prepared before 3,4 and their psychotropic properties described with human volunteers. However, no pharmacological studies on these new compounds have been carried out since then, aside from the few instances in which a β-methoxylated derivative has shown a potency similar to or slightly greater than that of the parent compound.

Little is known about the effects of substitution at the β-position of the side chain of hallucinogenic phenethylamines, although it was speculated that their activity might be mediated in part by interactions with adrennergic receptors.

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The nitro derivative 3j was obtained from the phenethylamine 3a, by nitration of the aromatic ring.

\[
\begin{align*}
\text{3a} & \xrightarrow{\text{HNO}_3} \text{3j} \\
\text{MeO} & \text{MeO} \\
\text{MeO} & \text{MeO} \\
\text{NH}_2 & \text{NH}_2
\end{align*}
\]

Iodination of the intermediate 2a gave the iodo derivative 2k, which was reduced to form the phenethylamine 3k.

\[
\begin{align*}
\text{2a} & \xrightarrow{[\text{I}^+]_2} \text{2k} \\
\text{MeO} & \text{MeO} \\
\text{NO}_2 & \text{NO}_2 \\
\text{MeO} & \text{MeO}
\end{align*}
\]

The use of anhydrous benzene as solvent for the nucleophilic addition 1 → 2 proved to be more convenient than the method previously described, which utilized the alcohol ROH as solvent 3,4, giving nitroethanes 2 in higher yields.

We generally performed the reduction step with AlH₃, generated in situ by partial neutralization of LiAlH₄ with concentrated sulfuric acid 8. However, in the case of the 2,4,5-trimethoxyphenyl intermediate 2g, this procedure led to hydrogenolysis of the β-methoxy substituent. Compound 3g, as its hydrochloride, could be obtained in 43% yield by reduction of 2g with lithium aluminum hydride in refluxing THF.

All β-alkoxyphenethylamines were purified and characterized by conversion into the corresponding hydrochloride salts.

The interactions of this series of compounds with 5-HT₂A/2C and α₁ receptors are currently under investigation in our laboratories.

A recent paper 9 suggested that the presence of an oxygenated substituent, such as an oxo or a hydroxy group, interposed between the aryl and the amino group of a number of serotonergic agonists, may enhance ligand selectivity for 5-HT₂A versus 5-HT₂C receptors. This observation and the scarcity of published data on β-substituted phenethylamines prompted us to prepare a series of new compounds which might prove more discriminating than the traditionally employed 5-HT₂A/2C agonists 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) 6 and 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB) 7.

Thus, the series of 1-aryl-1-alkoxy-2-aminoethanes 3 were prepared from the corresponding nitroethanes 1 by Michael addition of an alkoxide to the electrophilic double bond, followed by reduction of the resulting 1-alkoxy-2-nitroethanes 2.

\[
\begin{align*}
\text{1} & \xrightarrow{\text{RO}^-} \text{2} \\
\text{3}
\end{align*}
\]

(a) R = Me, X = H  
(b) R = Me, X = Br  
(c) R = Et, X = Br  
(d) R = Me, X = SPr  
(e) R = Me, X = Et  
(f) R = Me, X = Me

Experimental:

Melting points were obtained with a Kofler hot-stage apparatus and were not corrected.

1H nmr spectra were recorded on a Varian EM-360, 60 MHz instrument. All spectra utilized tetramethylsilane as internal reference.

The 1-aryl-2-nitroethenes 1 were prepared by base-catalyzed condensation of the corresponding benzaldehydes with nitromethane 4,9
Preparation of 1-Aryl-1-methoxy-2-nitroethanes. General Procedure—To a stirred, cooled (0-5°C) solution of the nitrophene 1 (10 mmol) in the appropriate volume of dry benzene under nitrogen were added 9.0 mL of a 3.3 M solution of sodium methoxide in methanol (prepared by the addition of 4.5 g of sodium to 60 mL of anhydrous methanol). After 5 minutes of reaction, the mixture was acidified with glacial acetic acid (15 mL), stirred for another 5 minutes and enough water was added to duplicate the initial volume.

The organic layer was then washed with water, the aqueous layer extracted with dichloromethane, the organic extracts combined, dried over CaCl₂ and evaporated to give the crude product in the form of a dark yellow oil that solidified on standing.

The product was then purified by flash chromatography, recrystallisation or bulb-to-bulb distillation.

The following compounds were prepared by this general procedure:

1-(2,5-Dimethoxyphenyl)-1-methoxy-2-nitroethane (2a) - 1a (8.8 g, 42 mmol) in dry benzene (80 mL) and the MeONa solution (3.3 M, 18 mL) gave, after purification of the crude product by flash chromatography (silica Merck 60H, chloroform as solvent), 9.4 g (93% yield) of 2a, mp 56-61°C. Anal. Calcld. for C₁₃H₁₂NO₃: C, 54.77; H, 4.62; N, 5.81. Found: C, 54.87; H, 4.77; N, 5.80. "H nmr (CDCl₃) δ 3.4 (3 H, s, β-OH), 3.8 (3 H, s, OMe), 3.9 (3 H, s, OMe), 4.4 (2 H, m, CH₂NO₂), 5.4 (1 H, m, β-CH), 6.9-7.1 (3 H, m, ArH).

1-(2,5-Dimethoxy-4-bromophenyl)-1-methoxy-2-nitroethane (2b) - 1b (5.0 g, 17 mmol) in dry benzene (70 mL) and the MeONa solution (3.3 M, 18 mL) gave, after recrystallisation in methanol, 3.9 g (72% yield) of 2b, mp 118-120°C, lit. 3 mp 119-120°C.

1-(2,5-Dimethoxy-4-bromophenyl)-1-ethoxy-2-nitroethane (2c) - 1b (3.6 g, 12.5 mmol) in dry benzene (50 mL) and an EONa solution (3.3 M, 11 mL) gave, after recrystallisation in ethanol, 3.3 g (79% yield) of 2c, mp 98-100°C. Anal. Calcld. for C₁₃H₁₆BrNO₃: C, 43.11; H, 4.79; N, 4.10. Found: C, 43.50; H, 4.40; N, 4.08. "H nmr (CDCl₃) δ 1.2 (3 H, t, J = 7 HZ, Me), 3.5 (2 H, q, J = 7 Hz, OCH₂), 3.6 (3 H, s, OMe), 3.9 (3 H, s, OMe), 4.5 (2 H, m, CH₂NO₂), 5.4 (1 H, m, β-CH), 5.5 (2 H, m, ArH), 7.0 (1 H, s, ArH), 7.1 (1 H, s, ArH).

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1-(2,5-Dimethoxy-4-thiopropoxyphenyl)-1-methoxy-2-nitroethane (2d) - 1d (3.1 g, 11 mmol) in dry benzene (50 mL) and the MeONa solution (3.3 M, 14 mL) gave, after recrystallisation in methanol, 3.3 g (95% yield) of 2d, mp 66-67°C. Anal. Calcld. for C₁₃H₁₃NO₅S: C, 53.33; H, 6.67; N, 4.44. Found: C, 53.34; H, 6.28; N, 4.18. "H nmr (CDCl₃) δ 1.0 (3 H, t, J = 7 Hz, Me), 1.7 (2 H, q, J = 7 Hz, CH₂), 3.8 (2 H, t, J = 7 Hz, CH₂S), 3.4 (3 H, s, β-OH), 3.8 (6 H, s, OMe), 4.4 (2 H, m, CH₂NO₂), 5.3 (1 H, m, β-CH), 6.8 (1 H, s, ArH), 6.9 (1 H, s, ArH).

1-(2,5-Dimethoxy-4-ethylphenyl)-1-methoxy-2-nitroethane (2e) - 1e (1.1 g, 4.6 mmol) in dry benzene (20 mL) and the MeONa solution (3.3 M, 4 mL) gave, after recrystallisation in ethanol, 1.0 g (80% yield) of 2e, mp 85-86.5°C. Anal. Calcld. for C₁₃H₁₄NO₃: C, 57.99; H, 7.06; N, 5.20. Found: C, 57.81; H, 6.99; N, 5.52. "H nmr (CDCl₃) δ 1.2 (3 H, t, J = 7 Hz, Me), 2.6 (2 H, q, J = 7 Hz, CH₂), 3.3 (3 H, s, β-OH), 3.8 (6 H, s, OMe), 4.4 (2 H, m, CH₂NO₂), 5.3 (1 H, m, β-CH), 6.6 (1 H, s, ArH), 6.8 (1 H, s, ArH).

1-(2,5-Dimethoxy-4-methylphenyl)-1-methoxy-2-nitroethane (2f) - 1f (1.0 g, 4.5 mmol) in dry benzene (20 mL) and the MeONa solution (3.3 M, 4 mL) gave, after recrystallisation in methanol, 0.8 g (70% yield) of 2f, mp 75-77°C, lit. 3 mp 78-79°C.

1-(2,4,5-Trimethoxyphenyl)-1-methoxy-2-nitroethane (2g) - 1g (3.7 g, 15 mmol) in dry benzene (40 mL) and the MeONa solution (3.3 M, 14 mL) gave, after recrystallisation in methanol, 3.6 g (68% yield) of 2g, mp 125-126°C. Anal. Calcld. for C₁₃H₁₇NO₅: C, 53.14; H, 6.27; N, 5.17. Found: C, 53.09; H, 6.47; N, 5.51. "H nmr (CDCl₃) δ 3.3 (3 H, s, β-OH), 3.8 (3 H, s, OMe), 3.9 (6 H, s, OMe), 4.4 (2 H, m, CH₂NO₂), 5.3 (1 H, m, β-CH), 6.7 (1 H, s, ArH), 7.1 (1 H, s, ArH).

1-(3,4-Methylenedioxyphenyl)-1-methoxy-2-nitroethane (2h) - 1h (5.0 g, 26 mmol) in dry benzene (60 mL) and the MeONa solution (3.3 M, 23 mL) gave, after bulb-to-bulb distillation (150°C/0.5 mmHg), 4.8 g (82% yield) of 2h, as a light yellow oil which slowly solidified, mp 57-58°C, lit. 3 mp 58-59°C.

1-(3,4,5-Trimethoxyphenyl)-1-methoxy-2-nitroethane (2i) - 1i (4.0 g, 17 mmol) in dry benzene (40 mL) and the MeONa solution (3.3 M, 15 mL) gave,
after recrystallization in methanol, 2.4 g (53% yield) of 21, mp 141-143
°C, lit 3 mp 145-144 °C.
1-(2,5-Dimethoxy-4-idophenyl)-1-methoxy-2-aminoresol (21) - To a
stirred mixture of silver trifluoracetate 10 (2.1 g, 9.5 mmol) and 1-(2,5-dimethoxyphenyl)-1-methoxy-2-aminoresol 21 (2.3 g, 9.5 mmol)
in dry chloroform (20 mL) was added dropwise, in the course of 2 hours, a
solution of Li 2 (2.4 g, 9.5 mmol) in chloroform (30 mL).

The reaction mixture was further stirred for 18 h. The precipitated
AgI was then filtered, and washed with chloroform. The organic filtrate
was then washed successively with aqueous NaHCO 3 (1.0 M), and with
water, and dried over anhydrous MgSO 4 . Evaporation of the solvent gave
3.4 g of a yellow solid, that was recrystallised in methanol to give 3.0 g
(66% yield) of product 21. mp 131-133.5 °C. Anal. Calcd. for C 11 H 14 NO 5 :
C, 55.97; H, 3.81; N, 3.81. Found: C, 56.08; H, 3.73; N, 3.47. 1 H nmr
(CDC 13 ) δ 3.5 (3 H, s, β-OMe), 4.6 (5 H, s, OMe), 4.7 (2 H, m, CH 2 NO 2 ), 5.6
(1 H, m, β-CH), 7.3 (1 H, s, ArH), 7.7 (1 H, s, ArH).

Reduction of 1-Aryl-1-alkoxy-2-aminoresol 2 General Procedure - To a
stirred, cooled (0-5 °C) suspension of LiAlH 4 (4.6 g, 120 mmol) in dry
THF (200 mL) was slowly added concentrated sulfuric acid (5.9 g, 60
mmol). The resulting mixture was stirred for 30 minutes and a solution of
the 1-aryl-1-alkoxy-2-aminoresol 2 (24 mmol) in the appropriate
volume of dry THF was then added. After stirring for 30 minutes at room
temperature, the mixture was gently refluxed for 2 hours. After cooling in
an ice-water bath, the excess hydride was decomposed by careful addition
of 2-propanol. A sodium hydroxide solution (15%) was then added until a
white precipitate was formed. This was filtered off and the filtrate
evaporated. The residue was redissolved in dichloromethane, and extracted
with dilute sulfuric acid (0.1 M). The aqueous extract was washed with
dichloromethane, basified with a sodium hydroxide solution (25%) and the
free amine extracted with CH 2 Cl 2 . After drying and evaporating the
solvent, the residue was purified by bulb-to-bulb distillation to give the
pure amine in the form of a colorless oil.

The amine was redissolved in a small amount of 2-propanol, and this
solution diluted with twice its volume of dry ethyl ether. Acidification
with drops of concentrated HCl, followed by overnight stirring of the
resulting solution precipitated the pure, crystalline hydrochloride of 3.
1-(2,4,5-Trime thoxyphenyl)-1-methoxy-2-aminothene hydrochloride (3gHCl) - The above reduction, performed with LiAlH4/H2SO4, led to the loss of the β-H2O group. The same procedure, employing 10 g (37 mmol) of the nitro compound 2g and LiAlH4 (0.7 g, 18 mmol) in dry THF (60 mL) gave, after the usual work-up, 0.4 g (45% yield) of the pure amine. The hydrochloride melted at 163-165 °C. Anal. Calcld. for C12H10N2O4.HCl: C, 51.89; H, 7.21; N, 5.04. Found: C, 51.60; H, 6.87; N, 5.23. 1H nmr (D2O) δ 3.0 (2 H, m, CH2N), 3.1 (3 H, s, β-OME), 3.6-3.7 (9 H, 3 s, OMe), 4.6 (1 H, m, β-CH), 6.6 (1 H, s, ArH), 6.8 (1 H, s, ArH).

1-(3,4-Methylenedioxy1-methoxy-2-aminothene hydrochloride (3hHCl) - 21% yield, mp 103-105 °C (hydrated form), mp 150 °C, lit 3 mp 152-153 °C. Anal. Calcld. for C10H13N03.HCl.H2O: C, 48.10; H, 6.41; N, 5.61. Found: C, 48.26; H, 6.19; N, 5.67.

1-(2,3,5-Trimethoxyphenyl)-1-methoxy-2-aminothene hydrochloride (3iHCl) - 37% yield, mp 196-197 °C, lit 3 mp 198.5-199.5 °C. Anal. Calcld. for C12H11NO3.HCl: C, 51.89; H, 7.21; N, 5.04. Found: C, 52.14; H, 7.21; N, 5.04.

1-(2,5-Dimethoxy-4-isodophenyl)-1-methoxy-2-aminothene hydrochloride (3kJHCl) - 38% yield, mp 215-217 °C. Anal. Calcld. for C11H16N03.HCl: C, 35.34; H, 4.55; N, 3.75. Found: C, 35.74; H, 4.20; N, 3.70. 1H nmr (D2O) δ 3.2 (2 H, m, CH2N), 3.4 (3 H, s, β-OME), 3.9 (3 H, s, OMe), 4.0 (3 H, s, OMe), 4.9 (1 H, m, β-CH), 7.0 (1 H, s, ArH), 7.6 (1 H, s, ArH).

1-(2,5-Dimethoxy-4-nitrophenoxy)-1-methoxy-2-aminothene hydrochloride (3kJHCl) - A solution of the hydrochloride of 1-(2,5-dimethoxyphenyl)-1-methoxy-2-aminothene (0.5 g, 2 mmol) in water (9 mL) was added with stirring and cooling (0-5 °C) to HNO3 (65%, 7 mL). After 5 minutes of stirring, the precipitated product nitrate was filtered and washed with water. The suspended salt in water (15 mL) was then treated with NaOH 5 M and the free base was extracted with dichloromethane (50 mL). After drying and evaporating the organic solvent, the residual yellow oil was purified in a bulb-to-bulb distillation apparatus (160 °C/0.4 mmHg). The pure amine was converted into its

hydrochloride by addition of drops of concentrated HCl to a solution of the base in 2-propanol/diethyl ether, forming 0.55 g (93% yield) of the product 3jHCl, mp 212-214 °C. Anal. Calcld. for C11H16N03.HCl: C, 45.13; H, 5.81; N, 9.57. Found: C, 44.70; H, 5.46; N, 9.31. 1H nmr (D2O) δ 3.2 (2 H, m, CH2N), 3.4 (3 H, s, β-OME), 3.9 (3 H, s, OMe), 4.0 (3 H, s, OMe), 5.0 (1 H, m, β-CH), 7.3 (1 H, s, ArH), 7.7 (1 H, s, ArH).

Acknowledgements: We are grateful to Brazilian CAPES for a grant to M.A.T.

References:


(Received in the USA 08 September 1994)